REMARKS

Claims 2-11 remain pending in this application. 1-8, 11, and 13 are rejected. Claim 12 is withdrawn. Claims 1, 12, and 13 are cancelled herein. Claims 2, 7, and 9 are amended herein to make them independent. Claim 3 is amended herein to remove the reference to claim 1, which has been cancelled. Also, claim 7 (as well as claims 8 and 9) is amended as suggested by the Examiner regarding the utility rejection.

Claims 1 and 3-7 have been rejected under 35 U.S.C. § 101. Claim 1 has been cancelled. Claims 3-6 now depend only from claim 2. Claim 7 has been made independent and the limitation of storing the information in a data file or in other form of digital memory has been added as suggested by the Examiner since the Office Action states on page 5 that the rejection can be overcome by amendment of the claims to recite an outputting to, for example, memory. A similar amendment was made to claims 8 and 9 for similar reasons. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn.

Claims 1 and 3-5 have been rejected under 35 U.S.C. § 102(b) as anticipated by Proc. Natl. Acad. Sci., Vol. 96, p. 11305-11310, September 1999 (Alm et al.). Claim 1 has been cancelled. Claims 3-5 now only depend from

claim 2. Accordingly, Applicants respectfully request that the rejection of claims 1 and 3-5 under 35 U.S.C. § 102(b) be withdrawn.

Claim 1 has been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 6,832,162 (Floudas et al.). Claim 1 has been cancelled. Accordingly, Applicants respectfully request that the rejection of claim 1 under 35 U.S.C. § 102(b) be withdrawn.

Claims 1-7 and 13 have been rejected under 35 U.S.C. § 103(a) as obvious over Floudas et al. in view of Alm et al.

Claims 1 and 13 have been cancelled, making their rejection moot.

The Office Action statest that Floudas et al. does not disclose, *inter alia*, predicting folding kinetics. The Office Action states that Alm et al. discloses predicting folding kinetics and that it would be obvious to combine Floudas et al. and Alm et al. such that the combination would include predicting folding kinetics. The Office Action states on page 9 that the reason for doing this is that "it simplifies the computation." The Supreme Court has explained the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). It is Applicants' position that the Office Action has not explained

how it is that including a prediction of folding kinetics in Floudas et al. would improve the computation of Floudas et al. It Applicants' position that *prima facie* obviousness has not been demonstrated since the conclusory statement of a simplification of computation, without more, does not provide a reason that would prompt one of ordinary skill in the art to make the combination.

Furthermore, to establish a *prima facie* case of obviousness, it is necessary to show that all the claim limitations are taught or suggested by the prior art. *See In re Royka and Martin*, 180 USPQ 580, 583, 490 F.2d 981 (CCPA 1974).

Claim 2 recites the following:

" C. applying the CLE model to said amino acid sequence and secondary structure information to evaluate the free energy of a combinatorial number of β-strand and α-helix arrangements as rapidly as polynomial time: $c(n-1)(n+1)$ wherein c is a constant and n is the number of secondary structure elements found in the said amino acid in step A and prepared in step B."

Claim 7 recites something very similar. The Office Action has not demonstrated that this element is found in Floudas et al. in view of Alm et al.

The Office Action seems to cite to column 10, lines 19-21 of Floudas et al. for this proposition. However, the sentence that includes column 10, lines 19-21 of Floudas et al., is the following: These complications have led to the development of threading methods, an NP-complete (complexity related to performance of nondeterministic Turing Machine in polynomial time) class of problems, in which the target sequence is threaded onto the backbone of the template sequence while evaluating the sequence fitness."

The cited portion of Floudas et al. fails to disclose the elements of step C. of claim 2 of the present application and very similar elements in claim 7. Accordingly, claims 2 and 7 are also patentable at least for this reason as well.

Moreover, Floudas et al. are saying that this cannot be done in polynomial time. An "NP complete problem" is one where every solution must be tested; i.e., it cannot be done in polynomial time. Neither does Alm et al. propose polynomial time. Alm et al. say 2^N (page 11305, column 2, line 25) where N is the number of amino acids in the sequence, which is known as exponential time. To reduce this number, they must first generate a list of all allowed configurations; a quantity proportional to order 2^N (page 11306, column 2, line 7) and then pursue solutions that can be improved by adding an additional amino acid (page 11306, column 2, lines 9-13) with unspecified

reduction of 2^N. These steps are not purported to be done in polynomial time. From there, they select out the best 100 structures and, in their fastest search, use a branch and bound algorithm to find the best solution (page 11306, column 2, lines 14-21). The branch and bound algorithm is known in the art to also require exponential time: about 1.26^N. Such calculation strategies as outlined here do not represent polynomial time in which the computational time should be proportional to N^j where j is significantly less than N (often less than 7). Alm et al. also admit that their strategy has problems (page 11307, columns 1 and 2). Therefore, they used the partition function equation (same page, column 2) to find the ensemble average structure rather than the minimum free energy. The present invention uses the minimum free energy, does not rely on an ensemble average structure, and uses a polynomial time algorithm to find that minimum free energy. Therefore, neither Floudas et al. nor Alm et al. disclose the elements of step C.

Additionally, please find attached a Declaration, which includes Appendices 1-3. In Appendix 1, part D) of the Declaration is a statement regarding *n* (which is recited in claims 2 and 7). This *n* pertains to secondary structure, not *N*, which is the total number of amino acids in the protein sequence. Floudas et al. and Alm et al. fail to disclose the *n*, as stated in

Appendix 1, part D) of the Declaration. Accordingly, claims 2 and 7 are also patentable for this reason as well.

Additionally, in Appendix 1, part B) of the Declaration are explained additional distinguishing characteristics between the present invention and Floudas et al. which further support the patentability of the present invention over Floudas et al. in view of Alm et al.

Furthermore, the reliance on combining Floudas et al. and Alm et al. to arrive at the claimed invention also has other problems in light of some differences between Alm et al. and the present invention as well as some other problems with Alm et al. In particular, the Office Action states on page 9 that it would have been obvious "to modify the method of Floudas et al. for predicting tertiary protein structures and topology with the method of Alm et al. for predicting protein folding from free energy landscapes." However, as described below, one of ordinary skill in the art would not have been prompted to make the combination of Floudas et al. and Alm et al.

The model used in Alm et al. only calculates the entropy for closing a loop, as explained in Appendix 1, part C) of the Declaration. The L_o in Alm et al. represents the closing of a loop of length L_o, not the total entropy loss due to forming structured regions of beta-strands into beta sheets. The Office Action

has not made clear why one of ordinary skill in the art would combine Alm et al. and Floudas et al. in light of this situation.

Furthermore, Alm et al. uses a lattice model that has numerous problems (see Appendix 1, part C) of the Declaration). In fact, the lattice model used in Alm et al. leads to a contradiction, as explained in Appendix 1, part C) of the Declaration and as shown in Appendix 2 of the Declaration. Accordingly, one of ordinary skill in the art would not be motivated to combine the invention of Floudas et al. and Alm et al. in light of the contradition of the lattice model of Alm et al.

Additionally, as explained in Appendix 1, part C) of the Declaration, the entropy model in Alm et al. is not an appropriate entropy model. Accordingly, this is a further reason why one of ordinary skill in the art would not combine Floudas et al. with Alm et al. to arrive a the claimed invention.

Also, the proposed folding purported in Alm et al. is not a reasonable comparison with the present invention. Alm et al. start with a completely determined structure and use this known information to "re-predict" their structure (Alm et al., page 11305, column 2, lines 21-27). The Office Action also refers to Alm et al. as using native-state topology (see also Alm et al., page 11305, column 1, last sentence). Thus, they have one correct solution and one

incorrect solution for each amino acid. This means that the lattice model in Alm et al. already has *all* the correct answers (including information about the turns) imported into the data set. Additionally, proteins do not fold in such a two state configuration situation as Alm et al. propose (one correct and one incorrect configuration). Proteins are not issued with one correct bond angle and one incorrect bond angle; the correct conformation at each bond must be discovered from infinitely main conceivably possible angles. Furthermore, in Appendix 1, part C, and Appendix 2 of the Declaration, such lattice-model approximations (as Alm et al. use) are shown to neglect degeneracy; they neglect the true number of distinguishable bond angles (known in the art as "Ramachandran angles") that are present in an amino acid sequence of number N. Whatever is speculated in Alm et al. beyond the "re-prediction" in Alm et al. is far more uncertain for a real problem where their loop information is missing. No reason has been identified by the Office Action that such a two state model with given structure information should be used in a true prediction problem. In contrast, the present invention does not assume the existence of such structure information and does not fold the structure using the two state prescription outlined by Alm et al. The present invention proposes grouping of amino acids based on the persistence length, where, due to the similarity of

length between protein secondary structure elements and the persistence length, amino acids are often also grouped in a complete protein secondary structure element. The structure is governed by constraints that are a function of the persistence length. Alm et al. group their model in an arbitrary grouping with their already given native state topology information. Neither Alm et al. nor Floundas et al. build their model on the persistence length. None of the computations in the present invention are simplified in the way described in Alm et al. as the present invention does not employ a lattice model and groups the amino acids by a persistence length. Nor do Alm et al use a global entropy, because the free energy calculates only the loop entropy with L_o which is shown to be erroneous in Appendix 3 of the Declaration. Accordingly, this demonstrates that the disclosure in Alm et al. is distinguishable from the present invention. Moreover, not only is Alm et al. distinguishable over the present invention, but also there is no reason to combine Alm et al. with Floudas et al. to arrive a the claimed invention.

Accordingly, for the aforementioned reasons, claims 2 and 7 are patentable over the cited art. Claims 3-6 are patentable at least for the reason that they depend from a patentable base claim. *See In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

Claims 8 and 11 have been rejected under 35 U.S.C. § 103(a) as obvious over Floudas et al., in view of Alm et al., and further in view of Dawson et al.

The Office Action statest that Floudas et al. does not disclose, *inter alia*, predicting folding kinetics. The Office Action states that Alm et al. discloses predicting folding kinetics and that it would be obvious to combine Floudas et al. and Alm et al. such that the combination would include predicting folding kinetics. The Office Action states on page 12 that the reason for doing this is that "Alm et al. show that a simple treatment of the interactions in a native protein is sufficient to account for most of the experimental data available on the folding of small protein domains" and that this "simplifies the computation." The Supreme Court has explained the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). It is Applicants' position that the Office Action has not explained how including a prediction of folding kinetics in Floudas et al. would improve the computation of Floudas et al. and how the prediction of folding kinetics is related to the statement that a simple treatment of interactions in a native protein is sufficient to account for most of

the experimental data available on the folding of small protein domains. It Applicants' position that *prima facie* obviousness has not been demonstrated since such conclusory statements, without more, do not provide a reason that would prompt one of ordinary skill in the art to make the combination.

Furthermore, to establish a *prima facie* case of obviousness, it is necessary to show that all the claim limitations are taught or suggested by the prior art. *See In re Royka and Martin*, 180 USPQ 580, 583, 490 F.2d 981 (CCPA 1974).

Claim 8 recites the following:

" D. applying the CLE model to said amino acid sequence and secondary structure information to reduce the combinatorial number of β-strand and α-helix arrangements."

The Office Action has not demonstrated that this element is found in Floudas et al. in view of Alm et al. and Dawson et al. Accordingly, claim 8 is also patentable at least for this reason as well.

Additionally, in the attached Appendix 1, part B) of the Declaration are explained additional distinguishing characteristics between the present invention and Floudas et al. which further support the patentability of the present invention over Floudas et al. in view of Alm et al. and further in view of

Dawson et al. Additional discussions are also presented regarding Alm et al. (Appendix 1, part C) and Dawson et al. (Appendix 1, part A).

Furthermore, the reliance on combining Floudas et al. and Alm et al. and Dawson et al. to arrive at the claimed invention also has other problems in light of some differences between Alm et al. and the present invention as well as some other problems with Alm et al. In particular, the Office Action states on page 9 that it would have been obvious "to modify the method of Floudas et al. for predicting tertiary protein structures and topology with the method of Alm et al. for predicting protein folding from free energy landscapes." However, as described below, one of ordinary skill in the art would not have been prompted to make the combination of Floudas et al. and Alm et al. and Dawson et al.

The model used in Alm et al. only calculates the entropy for closing a loop, as explained in Appendix 1, part C) of the Declaration. The L_o in Alm et al. represents the closing of a loop of length L_o, not the total entropy loss due to forming structured regions of beta-strands into beta sheets. Neither can it be called a "global entropy". In no way does it resemble the concepts outlined in Dawson et al. and in Appendix 1 (part A) and Appendix 3. The entropy model of Alm et al. is shown to be an erroneous entropy model. The Office Action has

not clarified why one of ordinary skill in the art would combine Alm et al. and Floudas et al. and Dawson et al. in light of this situation.

Furthermore, Alm et al. uses a lattice model that has numerous problems (see Appendix 1, part C) of the Declaration). In fact, the lattice model used in Alm et al. leads to a contradiction, as explained in Appendix 1, part C) of the Declaration and as shown in Appendix 2 of the Declaration. Also, Dawson et al. do not use a lattice model nor do they suggest one should do so to improve their calculations. Their model aims at finding the correct pairing structure of RNA based on the first principles from a thermodynamic model alone. Accordingly, one of ordinary skill in the art would not be motivated to combine the invention of Floudas et al. and Alm et al. and Dawson et al. in light of the contradition of the lattice model of Alm et al. and their entropy model.

Moreover, Dawson et al. do not understand that their entropy does not prevent crinkling-up effects that the local entropy control as a function of the persistence length (Appendix 1, part A). Neither do Alm et al or Floudas et al. recognize this problem. Dawson et al. assessed the results of their evaluation based upon given structures from other sources. They do not teach a method to find these same structures on their own without the aid of the sources of their structures. Were they to try to do so with their model as reported, they would

soon have discovered that their model ignored these local effects of entropy because their structures would have wrinkled up instead of straightened out as a function of the persistence length (as shown in Appendix 1, part A). Dawson et al. do not construct the secondary structures as a group either. Dawson et al. worked with *given* structures where such grouping was already provided. They cannot prop up their model without these selected data sets. Dawson et al. do not propose that these groups of RNA segments should be folded according to the number of ordered strand segments. Therefore, the present invention is distinguishable from Floudas et al. in view of Alm et al. and further in view of Dawson et al. at least because Dawson et al. do not know how to prevent the crinkling-up effects that this local entropy and group nature of the interaction in the persistence length control.

Additionally, as explained in Appendix 1, part C) of the Declaration, the entropy model in Alm et al. is not an appropriate entropy model. Accordingly, this is a further reason why one of ordinary skill in the art would not combine Floudas et al. with Alm et al. and Dawson et al. to arrive a the claimed invention.

Additionally, one of ordinary skill in the art would also not rely on Dawson et al. to combine it with Floudas et al. and Alm et al. in light of a

number of conceptual issues found in Dawson et al., as described in Appendix 1, part A) of the Declaration. For example, Dawson et al. does not solve the structure prediction problem and also fortuitously selected structures that agreed with the constraints in Dawson et al. in spite of errors.

Accordingly, for the aforementioned reasons, claim 8 is patentable over the cited art. Claim 11 is patentable at least for the reason that it depends from a patentable base claim. *See In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

Claims 9 and 10 were not rejected and Applicants deem those claims as being allowable. Claim 9 has been made independent to secure its allowance. Claim 10 depends from claim 9. It is respectfully requested that claims 9 and 10 be allowed.

Claim 2 was amended to be independent. Claim 7 was amended to be independent and to recite the storage of the information. Claim 8 was amended to recite the storage of the information. Claim 9 was amended to be independent and to recite the storage of the information. Support for the amendments of claims 2, 7, 8, and 9 are found, for example, in the claims as filed.

One further independent claim in excess of three is added. **The fee of $105.00 for the claim is provided for in the charge authorization presented**

in the PTO Form 2038, Credit Card Payment form, provided herewith.

Applicants respectfully request a two month extension of time for responding to the Office Action. **The fee of $230.00 for the extension is provided for in the charge authorization presented in the PTO Form 2038, Credit Card Payment form, provided herewith.**

If there is any discrepancy between the fee(s) due and the fee payment authorized in the Credit Card Payment Form PTO-2038 or the Form PTO-2038 is missing or fee payment via the Form PTO-2038 cannot be processed, the USPTO is hereby authorized to charge any fee(s) or fee(s) deficiency or credit any excess payment to Deposit Account No. 10-1250.

In light of the foregoing, the application is now believed to be in proper form for allowance of all claims and notice to that effect is earnestly solicited.

Respectfully submitted,
JORDAN AND HAMBURG LLP

By C. Bruce Hamburg
C. Bruce Hamburg
Reg. No. 22,389
Attorney for Applicants

and,

By Ricardo Unikel
Ricardo Unikel
Reg. No. 52,309
Attorney for Applicants

Jordan and Hamburg LLP
122 East 42nd Street
New York, New York 10168
(212) 986-2340

enc: Declaration (including Appendices 1, 2, and 3)
Form PTO-2038